

Amendments to the Specifications:

The original specification is replaced with the following substitute specification marked up to show changes. A clean copy of the substitute specification is enclosed as an attachment.

Please replace paragraph [[0012] with the following amended paragraph to the original specification:

[0012] In preferred embodiments, the delivery vehicle is a penetrating cream, the L-arginine is present as L-arginine hydrochloride (0.25 to 25%) in a concentration sufficient to produce the desired effect and the agent which creates the hostile biophysical environment is sodium chloride (0.25 to 25%) at a concentration sufficient to aid in tissue absorption.

Please cancel original paragraph [0014] and add new paragraph [0014.1]:

[0014.1] Nitric oxide causes increased local blood flow, which enables the growth of hair, which when applied to leg ulcers cause healing through use of the body's own mechanisms and when applied to a penis subject to erectile dysfunction causes restoration of normal sexual function. This effect is achieved by providing the biochemical

substrate at the local site from which the controlling substance, nitric oxide is produced. Nitric oxide causes increases in local blood flow allowing the body's own healing cells and substances to reach the ulcer site. A method for increasing the local blood flow in tissue of a mammal involves topically administering to the mammal an effective amount of a nitric oxide precursor. The nitric oxide precursor is administered in a delivery vehicle wherein the delivery vehicle is a penetrating cream, a liquid, a lotion, an ointment or other topical preparation and wherein the nitric oxide precursor is L-arginine a salt, a complex or a derivative thereof.

Please amend paragraph [0014] and renumber as [0014.2]:

[0014.2] ~~The preferred~~ One embodiment consists of a base cream with the properties of excellent absorption into the skin which also contains L-arginine hydrochloride (12.5% w/v), choline chloride (10%), sodium chloride (5% w/v) and magnesium chloride (5% w/v). The components of the base cream may be those commonly found in hand creams, such as water, mineral oil, glyceryl stearate, squalene, propylene glycol stearate, wheat germ oil, glyceryl stearate, isopropyl myristate, steryl stearate, polysorbate 60, propylene glycol, oleic acid, tocopherol acetate, collagen, sorbitan stearate, vitamin A & D, triethanolamine,

methylparaben, aloe vera extract, imidazolidinyl urea, propylparaben, and BHA.

Please add the following new paragraph after [0014.2]:

[0014.3] In another embodiment, the cream can comprise water (20-80%), mineral oil (3-18%), glyceryl stearate SE (0.5-12%), squalene (0.2-12%), cetyl alcohol (0.1-11%), propylene glycol stearate SE (0.1-11%), wheat germ oil (0.1-6%), glyceryl stearate (0.1-6%), isopropyl myristate (0.1-6%), stearyl stearate (0.1-6%), polysorbate 60 (0.1-5%), propylene glycol (0.05-5%), tocopherol acetate (0.05-5%), collagen (0.05-5%), sorbitan stearate (0.05-5%), vitamin A&D (0.02-4%), triethanolamine (0.01-4%), methylparaben (0.01-4%), aloe vera extract (0.01-4%), imidazolidinyl urea (0.01-4%), propylparaben (0.01-4%), bha (0.01-4%), L-arginine hydrochloride (0.25% to 25%), sodium chloride (0.25% to 25%), magnesium chloride (0.25% to 25%).

Please add the following new paragraph after [0014.3]:

[0014.4] An effective amount of a nitric oxide precursor is provided for increasing local blood flow in tissue. The nitric oxide precursor is L-arginine, a salt, a complex or a derivative thereof. An effective amount of nitric oxide precursor is L-arginine glutamate (0.25-25%). L-arginine

hydrochloride (0.25-25%) provides a precursor to the molecule, nitric oxide, NO. Nitric oxide is the substance that relaxes the blood vessels, allowing for increased blood flow. This invention relates to topical application of a cream, gel, or other vehicle which contains substances such as L-arginine which delivers these substances into tissue for the purpose of producing beneficial effects based on improvement of local blood supply.

Please add the following new paragraph after [0014.4]:

[0014.5] In another embodiment L-arginine further comprises a sufficient amount of ionic salt such as to create an ionic environment to cause absorption of the nitric oxide precursor. Choline chloride (0.25 to 25%), sodium chloride (0.25 to 25%) and magnesium chloride (0.25 to 25%) provides a high ionic strength environment for the highly charged molecule, L-arginine. This high ionic strength environment is an example of a hostile biophysical environment for L-arginine. That is, the highly charged ionic strength is an unfavorable environment for the highly charged L-arginine making the L-arginine anxious to move to a more hospitable, less charged environment such as human tissue. The base cream containing L-arginine (0.25 to 25%), choline chloride (0.25 to 25%), sodium chloride (0.25 to 25%) and magnesium chloride (0.25 to 25%) is the agent which produces

beneficial effects such as hair growth, healing of ulcers such as leg ulcers or restoration of normal erectile function in males suffering from erectile dysfunction.

Please replace paragraph [0015] with the following amended paragraph:

[0015] The cream, in another embodiment, acts effectively to induce hair growth on human scalp lacking sufficient hair when applied nightly to the bald area each night for several months. Hair growth is naturally a slow process. However, substantial hair growth is achieved over large areas of scalp with results becoming evident in a few weeks and substantial within several months. ~~Yet further, the cream acts to promote healing of superficial ulcers such as those sometimes found on the legs of persons with severe diabetes. Application twice daily for a period of two weeks causes substantial healing and in many cases complete healing is achieved within this time period or slightly longer (3-4 weeks).~~

Please add the following new paragraph after [0015]:

[0015.1] Yet further, the cream, in another embodiment, acts to promote healing of superficial ulcers such as those sometimes found on the legs of persons with severe diabetes.

Application twice daily for a period of two weeks causes substantial healing and in many cases complete healing is achieved within this time period or slightly longer (3-4 weeks). This invention relates to topical application of a cream, gel, or other vehicle which contains substances such as L-arginine which delivers these substances into tissue for the purpose of producing beneficial effects through restoration of natural mechanisms based on improvement of local blood supply.

Please add the following new paragraph after [0015.1]:

[0015.2] In another embodiment, the nitric oxide precursor may be administered with a trans-dermal patch, wherein the nitric oxide precursor is L-arginine, a salt, or a complex thereof. The trans-dermal patch, in another embodiment, can further comprise a sufficient amount of ionic salts such as to create an ionic strength environment to cause tissue absorption of the L-arginine species.

Please add the following new paragraph after [0015.2]:

[0015.3] Still further, in another embodiment, the cream acts to overcome erectile dysfunction in males causing restoration of natural sexual function. The method for overcoming impotence is by applying, through means of a

delivery vehicle to the penis, an effective dose of a precursor to the endothelial relaxing factor, nitric oxide. The delivery vehicle is a penetrating cream, a liquid, a lotion, and ointment or other topical preparation containing L-arginine, salt or salts of L-arginine, a complex of L-arginine or a derivative of L-arginine in an effective dose. In another embodiment, a complex of L-arginine or a derivative of L-arginine in an effective dose is combined with ionic salts such as to create an ionic strength environment high enough to provide an extra force to cause tissue absorption of the L-arginine species.

Please add the following new paragraph after [0015.3]:

[0015.4] These applications and others share as a common mechanism of action, improvement in local blood flow. A method for increasing local blood flow in tissue of a mammal is administering topically an effective amount of a nitric oxide precursor, wherein the nitric oxide precursor is either an L-arginine salt, complex or derivative thereof. An example providing an effective amount of nitric oxide precursor is by using L-arginine hydrochloride (0.25% to 25%) or L-arginine glutamate (0.25-25%). In the case of an alternative active agent were used it would be simply substituted for L-arginine in a delivery preparation. A sufficient amount of ionic salt such as to create an ionic

environment may be included to cause absorption of the
nitric oxide precursor.

Please replace paragraph [0017] with the following
amended paragraph to the original specification:

[0017] While L-arginine hydrochloride (0.25 to 25%) is the preferred active agent because it is the agent in nature itself, it is non-toxic, is highly soluble and it is inexpensive, other agents could be used which are also precursors or donors of nitric oxide. These include D,L - arginine, L-arginine, alkyl (ethyl, methyl, propyl, isopropyl, butyl, isobutyl, t-butyl) esters of L-arginine and salts thereof. Pharmaceutically acceptable salts include hydrochloride, glutamate, butyrate, and glycolate.

Please replace paragraph [0018] with the following
amended paragraph to the original specification:

[0018] In the case of an alternative active agent were used it would be simply substituted for L-arginine in a delivery preparation and the preparation used as in the case of the L-arginine preparation such as using either L-arginine hydrochloride (0.25 to 25%) or L-arginine glutamate (0.25 to 25%) instead of L-arginine.

Please replace paragraph [0020] with the following amended paragraph to the original specification:

[0020] A variety of means for effecting or improving absorption of the active agent can be envisioned, which are provided in the following several embodiments. One principle behind the absorption of a highly charged molecule such as L-arginine into tissue is to either create a biophysically hostile environment in the delivery vehicle such that L-arginine would prefer to be in tissue, or in an another embodiment is to package L-arginine in such a way that it is carried into tissue or neutralize its charge by derivitization or forming a neutral salt. Examples of biophysically hostile environments, include but are not limited to; high ionic strength by the addition of ionic salts such as sodium chloride, magnesium chloride or choline chloride; high or low pH by adding pharmaceutically acceptable acids or bases; and highly hydrophobic environments by decreasing water content and increasing lipid, oil and/or wax content. ~~Examples of packaging which would be carried into tissue includes liposomes or emulsions of collagen, collagen peptides or other components of skin or basement membrane. Examples of neutralization of charge include delivery of the active agent in the form or an ester or salt such as arginine glutamate which is electronically neutral. In each case of creating a hostile biophysical~~

~~environment for the active agent, the agent was added to an appropriate preparation.~~

Please add the following new paragraph after paragraph [0020]:

[0020.1] Examples of the other embodiment of packaging which would be carried into tissue includes liposomes or emulsions of collagen, collagen peptides or other components of skin or basement membrane. Examples of neutralization of charge include delivery of the active agent in the form or an ester or salt such as arginine glutamate which is electronically neutral. In each case of creating a hostile biophysical environment for the active agent, the agent was added to an appropriate preparation.

Please add the following new paragraph after paragraph [0020.1]:

[0020.2] In the case of creating a high ionic strength ions such as but not limited to sodium chloride, potassium chloride, choline chloride, magnesium chloride, lithium chloride, alone or in combination were added in high concentration. An example of a high concentration of high strength ions are sodium chloride (0.25% to 25%), choline

chloride (0.25% to 25%) and magnesium chloride (0.25% to 25%) alone or in combination.

Please add the following new paragraph after paragraph [0020.2]:

[0020.3] Other highly charged molecules such as polylysine, polyglutamine, polyaspartate or copolymers of such charged amino acids may be used to create the hostile biophysical environment. Alternatively a hostile biophysical environment may be created by placing the highly charged L-arginine in an hydrophobic, oily environment such as in an oil-based cream containing little or no water.

Please add the following new paragraph after paragraph [0020.3]:

[0020.4] Absorption may further be aided, in another embodiment, by combining the use of hostile biophysical environments with the use of penetrating agents such as oleoresin capsicum or its constituents or molecules containing heterocyclic rings to which are attached hydrocarbon chains.

Please add the following new paragraph after paragraph [0021]:

[0021.1] The method for promoting hair growth is to provide an effective dose of a nitric oxide precursor in a delivery vehicle, wherein the delivery vehicle is a penetrating cream, a liquid, a lotion, an ointment or other topical preparation. The cream can comprise water (20-80%), mineral oil (3-18%), glyceryl stearate SE (0.5-12%), squalene(0.2-12%), cetyl alcohol (0.1-11%), propylene glycol stearate SE (0.1-11%), wheat germ oil (0.1-6%), glyceryl stereate (0.1-6%), isopropyl myristate (0.1-6%), stearyl stearate (0.1-6%), polysorbate 60 (0.1-5%), propylene glycol(0.05-5%), tocopherol acetate (0.05-5%), collagen (0.05-5%), sorbitan stearate (0.05-5%), vitamin A&D (0.02-4%), triethanolamine (0.01-4%), methylparaben (0.01-4%), aloe vera extract (0.01-4%), imidazolidinyl urea (0.01-4%), propylparaben (0.01-4%), bha (0.01-4%), L-arginine hydrocholidide (0.25% to 25%), sodium chloride (0.25% to 25%), magnesium chloride (0.25-25%) and choline chloride (0.25-25%).

Please add the following new paragraph after paragraph

[0022]:

[0022.1] A method to overcome impotence is by applying, through means of a delivery vehicle to the penis, an effective dose of a precursor to the endothelial relaxing factor, nitric oxide. The delivery vehicle is a penetrating

cream, a liquid, a lotion, an ointment or other topical preparation containing L-arginine, salt or salts of L-arginine, a complex of L-arginine or a derivative of L-arginine in an effective dose.

Please add the following new paragraph after paragraph [0022.1]:

[0022.2] In another embodiment, the delivery vehicle in addition to the effective dose of L-arginine may contain ionic salts such as to create an ionic strength environment high enough to provide an extra force to cause tissue absorption of the L-arginine species.

Please add the following new paragraph after paragraph [0022.2]:

[0022.3] In another embodiment, the method for overcoming impotence has the delivery vehicle in the form of a cream that can comprise water (20-80%), mineral oil (3-18%), glyceryl stearate(0.25%-12%), squalene (0.2-12%), wheat germ oil (0.1-6%), cetyl alcohol (0.1-11%), propylene glycol stearate SE (0.1-11%), polysorbate 60(0.1-5%), propylene glycol (0.05-5%), vitamin E (0.02-4%), hyaluronic acid/collagen (0.05-5%), vitamin A& D (0.02-4%), sorbitan stearate (0.05-5%), triethanolamine(0.01-4%), imidazolidinyl

urea(0.01-4%), methylparaben(0.01-4%), propylparaben(0.01-4%) , bha 0.01-4%), aloe vera extract 0.01-4%), L-arginine hydrochloride (0.25% to 25%) and sodium chloride (0.25% to 25%), choline chloride (0.25-25%) and magnesium chloride (0.25-25%).

Please replace paragraph [0024] with the following amended paragraph:

[0024] Accordingly, it can be seen that in the present invention I have provided nitric oxide precursor agents, L-arginine and its derivatives, which when applied to scalp lacking sufficient hair causes hair growth through utilization of one of the body's own mechanisms. This effect is achieved by providing the biochemical substrate at the local site from which nitric oxide is produced. Nitric oxide causes increased local blood flow, which enables the growth of hair. ~~Further I have provided agents which when applied to leg ulcers cause healing through use of the body's own mechanisms. Still further I have provided agents that when applied to a penis subject to erectile dysfunction causes restoration of normal sexual function. This effect is achieved by providing the biochemical substrate at the local site from which the controlling substance, nitric oxide is produced. Nitric oxide causes increases in local blood flow~~

~~allowing the body's own healing cells and substances to reach the ulcer site.~~

Please add the following new paragraph after paragraph [0024]:

[0024.1] Further I have provided nitric oxide precursor agents, L-arginine and its derivatives, which when applied to leg ulcers cause healing through use of the body's own mechanisms. ~~Still further I have provided agents that when applied to a penis subject to erectile dysfunction causes restoration of normal sexual function.~~ This effect is achieved by providing the biochemical substrate at the local site from which the controlling substance, nitric oxide is produced. Nitric oxide causes increases in local blood flow allowing the body's own healing cells and substances to reach the ulcer site. A method for increasing local blood flow in tissue is administering topically an effective amount of a nitric oxide precursor, wherein the nitric oxide precursor is either an L-arginine salt, complex or derivative thereof. An effective amount of nitric oxide precursor is L-arginine hydrochloride (0.25% to 25%) or L-arginine glutamate (0.25-25%).

Please add the following new paragraph after paragraph [0024.1]:

[0024.2] Still further I have provided nitric oxide precursor agents, L-arginine and its derivatives, that when applied to a penis subject to erectile dysfunction causes restoration of normal sexual function.